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New (2,6-disubstituted-thiazol-5-yl)amine compounds useful for treating diseases e.g. osteoarthritis, multiple sclerosis, osteoporosis, asthma, cancer and graft rejection (Eng)
C2003-233032 R(AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR)
Addnl. Data: VERGNE F, BERNARDELLI P, LORTHIOIS E, DUCROT P

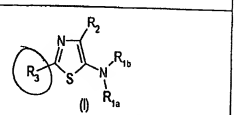
14-G1B, 14-G2A, 14-G2C, 14-G2D, 14-H1, 14-J1, 14-K1, 14-N1, 14-N4, 14-N11, 14-S1) .11

NOVELTY

(2,4-Disubstituted-thiazol-5-yl)amine compounds (I), their racemic forms, isomers, N-oxides, and their acidic or basic salt forms are new.

DETAILED DESCRIPTION

(2,4-Disubstituted-thiazol-5-yl)amine compounds of formula (I), their racemic forms, isomers, N-oxides, and their acidic or basic salt forms are new.



(I)

R_{1a} = H or (aryl)1-6C alkyl;

R_{1b} = (hetero)cycloalkyl, or (hetero)aryl (all optionally substituted by halo, trifluoromethyl, nitro, cyano, oxo, $-NR_4R_5$, $-CO_2R_4$, $-CONR_4R_5$, $-OR_4$, $-S(O)_nR_4$, $-S(O)_nR_4R_5$, tetrazolyl or 1-6C alkyl (optionally mono- - tri-substituted by $-OR_4$, $-NR_4R_5$ or $-CO_2R_4$));

n and m = 0 - 2;

R_4 and R_5 = H or $-X_1R_6$;

X_1 and X_2 = single bond or 1-6C alkylene;

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R_4 = 1-6C alkyl, (hetero)cycloalkyl or (hetero)aryl;

R_5 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, aryl or cycloalkyl;

R_3 = (hetero)cycloalkyl or (hetero)aryl (all optionally substituted by halogen, nitro, cyano, trifluoromethyl, oxo, 1-6C alkyl, $-OR_6$, $-NR_6R_7$, $-COR_6$, $-CO_2R_6$, $-CONHOH$, $-CONR_6R_7$, $-S(O)_nR_6$, $-S(O)_m-NR_6R_7$, $-NR_6COR_7$, $-NR_6SO_2R_7$, $-N(SO_2R_7)_2$, $-NR_6-CO-NR_7R_8$ or tetrazolyl;

R_6 and R_7 = H or $-X_2R_8$;

R_8 = 1-6C alkyl, (hetero)cycloalkyl or (hetero)aryl (all optionally mono- - tri-substituted by OH, 1-6C alkoxy, 1-6C alkyl, amino, mono-1-6c alkylamino, di-1-6C alkylamino, carboxy, 1-6C alkoxycarbonyl or benzyl; and

R_8 = H or 1-6C alkyl.

The aryl is an aromatic monocyclic or bicyclic system containing 5-10C; in the bicyclic ring system, one of the rings is aromatic and the other ring is optionally aromatic or partially hydrogenated and when the second ring is partially hydrogenated, then the ring is optionally mono- or di-substituted by oxo. The heteroaryl is the aryl group in which 1 - 4 carbon atoms are replaced by 1 - 4 heteroatoms selected from O, S and N. The cycloalkyl is a monocyclic or polycyclic system containing 3 - 10C and is saturated or partially unsaturated but without aromatic character and in the polycyclic system, each cycle could be fused together or formed a link. The heterocycloalkyl is the cycloalkyl group in which 1 - 4 carbon atoms are replaced by 1 - 4 heteroatoms selected from O, S or N.

An INDEPENDENT CLAIM is included for preparation of (I).

ACTIVITY

Immunosuppressive; Antiinflammatory; Respiratory-Gen.; CNS-Gen.; Antiallergic; Gastrointestinal-Gen.; Analgesic; Osteopathic; Neuroprotective; Antiasthmatic; Cytostatic; Anti-HIV; Antiarthritic.

MECHANISM OF ACTION

Phosphodiesterase-7 (PDE-7) inhibitor.

(I) were tested for inhibition of cyclic nucleotide phosphodiesterase 7, as given in W.J.Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol.10:69 - 92, ed.G.Brooker et al. Raven Press, NY. They showed IC_{50} value of 0.02 - 100 micro M. No results for specific compounds are given.

USE

For the treatment of a disease including T-cell related disease, autoimmune disease, inflammatory disease, respiratory disease, CNS

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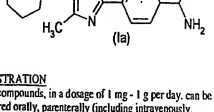
disease, allergic diseases, endocrine or exocrine pancreas disease, gastrointestinal diseases, visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease (COPD), allergic rhinitis, asthma, cancer, acquired immune deficiency syndrome (AIDS) and graft rejection (claimed).

ADVANTAGE

The compounds are active at very low concentrations.

SPECIFIC COMPOUNDS

4 Compounds (I) are specifically claimed, e.g. 7-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]quinazoline-4-amine (Ia).



(Ia)

ADMINISTRATION

The compounds, in a dosage of 1 mg - 1 g per day, can be administered orally, parenterally (including intravenously, intramuscularly or subcutaneously), per- or trans-cutaneously, intravaginally, rectally, nasally, perlingually, buccally, ocularly or by respiratory route.

EXAMPLE

To a solution of 4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid in tetrahydrofuran (THF) was added 1,1'-carbonyldiimidazole (1.2

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(con't)

equivalents) and the mixture was stirred for 30 minutes. The (S)-2-alanine tert-butyl ester was added and the mixture was stirred for 24 hours. The solvent was removed and the residue was worked up to obtain tert-butyl(2S)-2-[[(4-oxo-3,4-dihydroquinazolin-7-yl)carbonyl]amino]propanoate (A).

(A) was added to a solution of 5% trifluoroacetic acid in dichloromethane and the mixture was stirred for 3 hours, followed by a work-up to obtain (2S)-2-[[(4-oxo-3,4-dihydroquinazolin-7-yl)carbonyl]amino]propanoic acid (A1).

To a solution of (A1) in THF, 1,1'-carbonyldiimidazole (1.2 equivalents) was added and the mixture was stirred for 30 minutes. Then the cyclohexylamine was added and the mixture was stirred for 24 hours, followed by a work-up to obtain N-[(1S)-2-(cyclohexylamino)-1-methyl-2-oxoethyl]-4-oxo-3,4-dihyroquinazoline-7-carboxamide (A2).

To a solution of (A2) in pyridine was added Lawesson's reagent and the mixture was heated to 100°C for 6 hours. After cooling to room temperature, saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture and the product was worked up to obtain 7-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]quinazoline-4(3H)thione (A3).

To a stirring solution of (A3) and potassium carbonate (1.2 equivalents) in methanol was added CH3I. After 30 minutes, the solvent was removed to obtain N-cyclohexyl-4-methyl-2-[4-(methylthio)quinazolin-7-yl]-1,3-thiazol-5-amine (A4).

A solution of (A4) in saturated butanolic ammonia was sealed in steel bomb and heated at 100°C for 2 days. The solvent was removed and the residue was purified to obtain 7-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]quinazoline-4-amine (1a).

DEFINITIONS

Preferred Definitions:

R_{1a} = H;

R_{1b} = cyclohexyl group (optionally mono-substituted by OH) or phenyl (optionally mono-substituted by tetrazolyl or $-CO_2R_x$);

R_4 = H or 1-6C alkyl;

R_3 = methyl;

R_2 = quinoxalinyl, 1H-quinazolinyl, 3H-quinazolinyl-4-one, 1H-quinazolinyl-2,4-dione (all optionally mono- tri-substituted by halo, 1-6C alkyl, OR_x or NR_xR_y);

X_2 = single bond;

R_b = 1-6C alkyl (optinally monosubstituted by OH, 1-6C alkoxy, amino, mono-1-6C alkylamino or di-1-6C alkylamino.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation (Claimed): Preparation of (I) involves:

(1) coupling a carboxylic acid of formula R_3-C(=O)OH with an amine of formula ProtO-C(=O)-CHR_2)-NH_2 under peptidic coupling conditions to give a coupled product of formula R_3-C(=O)-NH-$CH(CO_2Prot)$-R_2;

(2) deprotecting the coupled product by treatment with an acid or base to give a free carboxylic acid compound of formula R_3-C(=O)-NH-$CH(CO_2H)$-R_2 (V);

(3) reacting (V) with a primary amine of formula R_{1b}-NH_2 under peptidic coupling conditions in the presence of a coupling agent to give a couple product of formula R_3-C(=O)-NH-$CH(R_2)$-C(=O)-$NH(R_{1b})$ (VI);

(4) treating (VI) with Lawesson's reagent in basic medium to give (I) (in which R_{1a} is H);

(5) treating (I) (in which R_{1a} is H) with R'_{1a}-L_1 to give(I) (in which R_{1a} is R'_{1a}) optionally under alkaline medium;

(6) purifying (I) (in which R_{1a} is H or R'_{1a}) by a conventional purifying technique; and

(7) separating into their respective isomers, followed by converting into their salts with acid or base or into N-oxide.

Prot = protective group of carboxylic acid group;

R'_{1a} = (aryl)1-6C alkyl;

L' = leaving group.

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